Epidermal growth factor suppresses intestinal epithelial cell shedding through a MAPK-dependent pathway.

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Public Summary:
Cell shedding from the intestinal villus is a key element of tissue turnover that is essential to maintain health and homeostasis. However, the signals regulating this process are not well understood. We asked whether shedding is controlled by epidermal growth factor receptor (EGFR), an important driver of intestinal growth and differentiation. In 3D ileal enteroid culture and cell culture models (MDCK, IEC-6 and IPEC-J2 cells), extrusion events were suppressed by EGF, as determined by direct counting of released cells or rhodamine-phalloidin labeling of condensed actin rings. Blockade of the MEK-ERK pathway, but not other downstream pathways such as phosphoinositide 3-kinase (PI3K) or protein kinase C (PKC), reversed EGF inhibition of shedding. These effects were not due to a change in cell viability. Furthermore, EGF-driven MAPK signaling inhibited both caspase-independent and -dependent shedding pathways. Similar results were found in vivo, in a novel zebrafish model for intestinal epithelial shedding. Taken together, the data show that EGF suppresses cell shedding in the intestinal epithelium through a selective MAPK-dependent pathway affecting multiple extrusion mechanisms. EGFR signaling might be a therapeutic target for disorders featuring excessive cell turnover, such as inflammatory bowel diseases.

Scientific Abstract:
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